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Report No. 12-34

This research was conducted in compliance with all applicable federal regulations governing the protection of human subjects in research.

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Safety of the Pandemic H1N1 Influenza Vaccine Among Pregnant U.S. Military Women and Their Newborns

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OBJECTIVES: To assess adverse pregnancy outcomes among active-duty U.S. military women who received pandemic H1N1 vaccine during pregnancy as well as adverse health outcomes among the newborns resulting from these pregnancies.

METHODS: The primary study population was a retrospective cohort of active-duty U.S. military women vaccinated during pregnancy with either the pandemic H1N1 vaccine between October 2009 and June 2010 or with seasonal influenza vaccine between October 2008 and June 2009. Rates of pregnancy loss, preeclampsia or eclampsia, and preterm labor were compared between pandemic H1N1 vaccine-exposed (n=10,376) and seasonal influenza vaccine-exposed pregnancies (n=7,560). A secondary study population consisted of newborns resulting from these pregnancies. Rates of preterm birth, birth defects, fetal growth problems, and the male-to-female sex ratio were compared between newborns exposed to pandemic H1N1 vaccine and newborns exposed to seasonal influenza vaccine in utero.

RESULTS: No significant differences were observed in rates of pregnancy loss (6.4% compared with 6.5%), preeclampsia or eclampsia (5.8% compared with 5.2%), or preterm labor (6.5% compared with 6.2%) between pandemic H1N1 vaccine-exposed and seasonal influenza vaccine-exposed pregnancies. Furthermore, no significant differences were observed in rates of preterm birth (6.2% compared with 6.3%), birth defects (2.1% compared with 2.0%), fetal growth problems (2.6% compared with 2.4%), or the male-to-female sex ratio (1.05 compared with 1.07) between newborns exposed in utero to pandemic H1N1 vaccine compared with seasonal influenza vaccine. Rates of all outcomes were lower or similar to overall general population rates. This study had at least 80% power to detect hazard ratios of 1.18–1.21 or odds ratios of 1.10–1.36, depending on outcome prevalence.

CONCLUSION: No adverse pregnancy or newborn health outcomes associated with pandemic H1N1 vaccination during pregnancy were noted among our cohort. These findings should be used to encourage increased vaccine coverage among pregnant women.

(Obstet Gynecol 2013;121:511–8)
DOI: http://10.1097/AOG.0b013e318280d64e

LEVEL OF EVIDENCE: II

See related editorial on page 503.

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The authors thank LTC Patrick Garman from the Military Vaccine Agency, Falls Church, Virginia, for his consultation on military vaccine issues; Gia Gumbs, Kathy Snell, and Isabel Jacobsen from the Department of Defense Birth and Infant Health Registry for their participation in study background discussions as well as administrative support; Dr. Don Slymen from the Naval Health Research Center, San Diego, California, for his consultation on the statistical analyses; and Beverly Sheppard and Michelle LeWark from the Naval Health Research Center, San Diego, California, for administrative support and copyediting. The authors appreciate the support of Eileen Hruska and the Defense Manpower Data Center, Seaside, California, with vaccine data access and management.

Presented at the National Vaccine Safety Task Force H1N1 Vaccine Safety Risk Assessment Working Group, August 22, 2011, through teleconference from San Diego, California; the World Health Organization Global Advisory Committee on Vaccine Safety Meeting, December 7–8, 2011, Geneva, Switzerland (through teleconference from San Diego, California); and the 2012 San Diego Epidemiology Research Exchange, April 27, 2012, San Diego, California.

This work represents report number 12-34, financially supported by the U.S. Department of Defense and the Military Vaccine Agency, under work unit numbers 60504 and N1222. The content and views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, the Department of the Army, the Department of the Air Force, the Department of Defense, the Department of Veterans Affairs, or the U.S. government. Approved for public release; distribution is unlimited. This research was conducted in compliance with all applicable federal regulations governing the protection of human subjects in research (protocol NHRC.2010.0006).

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Financial Disclosure
The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/13

In April 2009, a novel strain of influenza A virus, now known as pandemic influenza H1N1, emerged in the

United States.[1] As with both seasonal and pandemic influenza in the past, pregnant women were at greater risk for influenza-related complications from this new virus.[2,3] The Advisory Committee on Immunization Practices recommended that pregnant women be included in the initial target group for immunization with the inactivated injectable pandemic H1N1 vaccine.[4] Because the manufacturing process for the 2009 pandemic H1N1 vaccine was similar to that of seasonal influenza vaccine, which has an excellent safety record, a comparable safety profile was expected.[5]

Despite this expectation, and in light of the excess risk of Guillain-Barré syndrome that suspended the swine influenza vaccination program in 1976,[6] federal vaccine safety monitoring systems were expanded to ensure that any unforeseen safety problems would be rapidly identified. No major safety problems have been detected with the 2009 pandemic H1N1 vaccine in the general population. Studies specifically addressing vaccine safety during pregnancy are reassuring to date but are limited to passive surveillance system data,[7,8] a few small observational studies,[9–12] and several larger recent non-U.S.–based studies.[13–15]

Because influenza vaccination is compulsory for active-duty U.S. military personnel, all pregnancies among military women actively serving during the 2009–2010 vaccination campaign had a high likelihood of exposure to this novel vaccine. We used data from this large cohort of women who received pandemic H1N1 vaccination during pregnancy to examine the affect of this vaccine on maternal and newborn health outcomes.

POPULATION AND METHODS

We performed a retrospective cohort study of adverse pregnancy outcomes among active-duty U.S. military women vaccinated during pregnancy with either the pandemic H1N1 vaccine between October 2009 and June 2010 or with seasonal influenza vaccine between October 2008 and June 2009 and adverse health outcomes among the newborns resulting from these pregnancies. This research was conducted in compliance with all applicable federal regulations governing the protection of human subjects in research. Institutional review board approval was obtained from the Naval Health Research Center; informed consent was waived in accordance with criteria set forth by 32 CFR 219.

This study used methodology from the Department of Defense Birth and Infant Health Registry.[16] Data from the Department of Defense Manpower Data Center were used to identify active-duty women who received the pandemic H1N1 vaccine with or without the seasonal influenza vaccine during the 2009–2010 season or the seasonal influenza vaccine during 2008–2009. Among these women, pregnancies and associated outcomes were identified using the Department of Defense Military Health System Data Repository.

The Military Health System Data Repository contains International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)-coded and Current Procedural Terminology (CPT)-coded medical diagnoses and procedures for Department of Defense-sponsored inpatient and outpatient health care encounters at military and civilian facilities. Using pregnancy-related ICD-9-CM and CPT codes, complex algorithms were developed to define pregnancies. For pregnancies ending in a live delivery, estimated gestational age at birth was based on ICD-9-CM codes from the newborn birth record (weeks of gestation: 765.2 [1–9]; preterm birth: 765.[0,1]x; postterm newborn: 766.2x; multiple birth: V3[1,2,3,4,5,6].xx) or the maternal delivery record (preterm delivery: 644.2x; postterm pregnancy: 645.[1.2]x; multiple gestation or delivery: 651.xx, V27.[2,3,5,6]x).

Pregnancy onset was defined as the estimated date of the last menstrual period calculated by subtracting estimated gestational age at birth from the date of delivery. For pregnancies not ending in a live delivery, last menstrual period was calculated by subtracting 50 days (the median time from last menstrual period to start of pregnancy care for pregnancies ending in a live delivery) from the beginning date of pregnancy care. End of pregnancy was defined as the newborn's date of birth or, for pregnancies ending in a loss, the date of first record of pregnancy loss. Data on liveborn neonates resulting from these pregnancies were obtained by linking pregnancy episodes to V3x.xx-coded neonatal hospital discharge records as per current Department of Defense Birth and Infant Health Registry methodology.[17]

For the present study, the exposed group included active-duty military women who received the pandemic H1N1 vaccine (strain A/California/7/2009 [H1N1]) during pregnancy between October 1, 2009, and June 30, 2010. The comparison group included active-duty military women who received the 2008–2009 seasonal influenza vaccine (A/Brisbane/59/2007 [H1N1]-like virus, an A/Brisbane/10/2007 [H3N2]-like virus, and a B/Florida/4/2006-like virus) during pregnancy between October 1, 2008, and June 30, 2009. Pregnancies exposed to both pandemic H1N1 vaccine and 2008–2009 seasonal influenza vaccine were included in the pandemic H1N1-exposed group but not the comparison group. Pregnancies in the pandemic H1N1

group may have also been exposed to the 2009–2010 seasonal influenza vaccine on the same or a different day. A vaccination was considered to have been received during pregnancy if administered on or after the estimated last menstrual period through the day before the end of pregnancy. A secondary population included newborns born as a result of the pandemic H1N1-exposed pregnancies and seasonal influenza-exposed comparison pregnancies.

Maternal outcomes assessed in this study included pregnancy loss, preeclampsia or eclampsia, and preterm labor. Pregnancy loss was determined from ICD-9-CM diagnostic (ectopic or molar pregnancy: 630.xx–633.xx; other pregnancy with abortive outcome: 634.xx–639.xx; intrauterine death: 656.4x; outcome of delivery: V27.[1,3,4,6,7]) and procedure codes (removal of ectopic/molar pregnancy: 66.62, 68.0, 74.3) and CPT procedure codes (treatment of molar or ectopic pregnancy: 59100, 59120, 59121, 59130, 59135, 59136, 59140, 59150, 59151, 59870) indicating a pregnancy loss. Pregnancies ending in elective abortions were excluded from analyses.

Preeclampsia or eclampsia cases were defined as pregnancies with an ICD-9-CM-coded diagnosis of preeclampsia (642.4x–642.7x) occurring during pregnancy with initial diagnosis at least 1 day after pandemic H1N1 or seasonal influenza immunization. Additional requirements included an inpatient diagnosis, a diagnosis after 20 weeks of gestation, and a diagnosis overlapping the delivery or loss episode. Because preeclampsia typically does not develop until after 20 weeks of gestation, pregnancies ending before this point could not develop this outcome and were excluded from these analyses. Pregnancies with an initial preeclampsia or eclampsia diagnosis date on the same date as the pandemic H1N1 or seasonal influenza immunization were also excluded.

Preterm labor cases were defined as pregnancies with an ICD-9-CM-coded diagnosis of threatened premature labor (hereafter referred to as premature labor; 644.0x) or early (spontaneous) onset of delivery (hereafter referred to as premature delivery; 644.2x) occurring during pregnancy with initial diagnosis of either premature labor or premature delivery at least 1 day after pandemic H1N1 or seasonal influenza immunization. For premature labor cases, in the absence of premature delivery, an inpatient diagnosis of premature labor was required and initial diagnosis had to occur between 22 and 37 weeks of gestation. For premature delivery cases, initial diagnosis of premature labor or premature delivery had to occur after 22 weeks of gestation and a diagnosis of premature delivery was required during the delivery (or loss) episode. Furthermore, for premature delivery cases resulting in a liveborn neonate, evidence of preterm birth was required. Because preterm labor is not typically diagnosed before 22 weeks of gestation, pregnancies ending before this point could not develop this outcome and were excluded from analyses. Similarly, preterm labor cannot occur after 37 weeks of gestation; therefore, pregnancies with a pandemic H1N1 or seasonal influenza immunization after this point could not develop this outcome and were excluded. Pregnancies with an initial premature labor or premature delivery diagnosis date on the same date as the pandemic H1N1 or seasonal influenza immunization were excluded as were multiple-gestation pregnancies.

Newborn outcomes assessed in this study included preterm birth, birth defects diagnosed at birth, fetal growth problems, and male-to-female sex ratio. Preterm birth was assessed using a newborn's estimated gestational age at birth. Newborns born at an estimated gestational age of less than 37 completed weeks were considered preterm. Multiple births were excluded from this analysis. To identify newborns with birth defects diagnosed at birth, the inpatient newborn birth records were evaluated using the case definition from the National Birth Defects Prevention Network,[18] which uses ICD-9-CM codes for congenital anomalies (740.xx–760.xx). Cases of atrial septal defect (745.5x) and patent ductus arteriosus (747.0x) in preterm newborns were not included as birth defects in accordance with Metropolitan Atlanta Congenital Defects Program guidelines.[19] To identify newborns with fetal growth problems, these same records were evaluated for the presence of ICD-9-CM codes for slow fetal growth and fetal malnutrition (764.0x, 764,1x, 764.2x, 764.9x). The male-to-female sex ratio was evaluated as an overall indicator of reproductive health and a potential surrogate assessment of pregnancy loss.[20,21]

Maternal demographic and military personnel data were obtained from the Defense Manpower Data Center and reflected maternal status at the end of pregnancy with the exception of maternal age, described subsequently. These data included maternal birth date, race and ethnicity, marital status, service branch, military rank, and military occupation.

Calculation of maternal age differed between the maternal and newborn outcome models. For the maternal outcome analyses, maternal age was calculated at the woman's estimated date of delivery (calculated as last menstrual period+280 days), because pregnant women are clinically managed according to their age at estimated date of delivery, which could influence diagnosis of some pregnancy outcomes. For

the pregnancy loss and preterm labor models, maternal age was categorized as younger than 35 years or 35 years or older.[22] Because both younger and older women are considered to be at greater risk for preeclampsia or eclampsia, maternal age for this outcome was categorized as younger than 20 years, 20–40 years, or older than 40 years.[23,24] For the newborn outcome analyses, maternal age was calculated at the time of the newborn's birth and categorized as younger than 35 years or 35 years or older.

For each outcome of interest, descriptive statistics of maternal characteristics, stratified by vaccine type, were generated. Univariable analyses were performed to assess the significance of associations between vaccine receipt and the outcomes of interest. Multivariable models were built and assessed for possible confounding, collinearity, fit, and significant associations. Confounders were defined as those variables resulting in 15% or greater change in the measure of association between the exposure and outcome of interest. Collinearity was assessed using the variance inflation factor with a value of 4.0 or greater indicating possible multicollinearity between variables. Model fit was assessed using the Grønnesby and Borgan goodness-of-fit test for Cox proportional hazards models[25] and the Hosmer-Lemeshow goodness-of-fit test for logistic regression models.[26]

To assess the maternal outcomes of pregnancy loss, preeclampsia or eclampsia, and preterm labor, Cox proportional hazards regression was used to compare the adjusted hazard of each outcome between pandemic H1N1 vaccine-exposed pregnancies compared with 2008–2009 seasonal influenza vaccine-exposed pregnancies while controlling for several demographic and service-related variables. Data were left-truncated at the date of immunization to account for timing of vaccination during pregnancy. Data were also right-censored at the end of pregnancy for pregnancies not experiencing the outcome of interest. Follow-up time was measured from last menstrual period until the outcome date or censor date.

To assess the newborn outcome of preterm birth, Cox proportional hazards regression was used using similar methodology described for the maternal outcomes. The newborn outcomes of birth defects (diagnosed at birth), fetal growth problems, and newborn male-to-female sex ratio were evaluated using multivariable logistic regression models to estimate the adjusted odds of each outcome among newborns born to women who received pandemic H1N1 vaccine during pregnancy compared with those born to women who received 2008–2009 seasonal influenza vaccine during pregnancy. Analyses were adjusted for maternal demographic and service-related variables as well as timing of vaccine administration (during the first trimester [between last menstrual period and last menstrual period+91 days] compared with after the first trimester).

Post hoc power analysis, using an α of 0.05 and observed outcome prevalences in the control groups, demonstrated that this study had at least 80% power to detect hazard ratios of 1.18–1.21 (pregnancy loss, preeclampsia or eclampsia, preterm labor, and preterm birth outcomes) or odds ratios of 1.10–1.36 (birth defects, fetal growth problems, and male-to-female newborn sex ratio outcomes) depending on outcome prevalence. Data management and statistical analyses were performed using SAS software 9.2.

RESULTS

During the 2009–2010 season, over 80% of more than 250,000 active-duty women received the pandemic H1N1 vaccine, and 10,896 pregnancies occurred among women who received the vaccine while pregnant. After excluding pregnancies with unknown outcomes (n=492) and those ending in elective abortion (n=28), 10,376 pregnancies remained (Table 1). Vaccination occurred during the first trimester in 4,122 (39.7%) of the pregnancies. The vast majority of pregnancies (97.4%) were exposed to the injectable pandemic H1N1 vaccine, and most (64.4%) were also exposed to seasonal influenza vaccine, although usually on a different day. Pregnancies resulted in 9,710 (93.6%) live deliveries and 666 (6.4%) pregnancy losses. In the comparison group of more than 225,000 active-duty women, approximately 75% received the 2008–2009 seasonal influenza vaccine, and 8,017 pregnancies were identified among women who received the vaccine during pregnancy. After excluding pregnancies with unknown outcomes (n=433) and those ending in elective abortion (n=24), 7,560 pregnancies remained (Table 1). Vaccination occurred during the first trimester in 2,745 (36.3%) of the pregnancies. Most pregnancies (79.7%) were exposed to the injectable vaccine. Pregnancies resulted in 7,071 (93.5%) live deliveries and 489 (6.5%) pregnancy losses. Demographic characteristics of the women among whom these pregnancies occurred are shown in Table 1.

Multivariable models were created for each pregnancy and newborn outcome. Assessments for each model did not reveal multicollinearity, and each model demonstrated a good fit. There was no significant difference in the number of pregnancy losses among 2009–2010 pandemic H1N1 vaccine-exposed pregnancies compared with 2008–2009 seasonal

Table 1. Characteristics of Pregnancies and Neonates of Women Who Received 2009–2010 Pandemic H1N1 Vaccine or 2008–2009 Seasonal Influenza Vaccine During Pregnancy

Characteristic	Pregnancies		Neonates	
	Pandemic H1N1 Vaccine Group	2008–2009 Seasonal Influenza Vaccine Group	Pandemic H1N1 Vaccine Group	2008–2009 Seasonal Influenza Vaccine Group
Total	10,376 (100.0)	7,560 (100.0)	9,435 (100.0)	6,759 (100.0)
Exposure timing				
After first trimester	6,254 (60.3)	4,815 (63.7)	6,011 (63.7)	4,563 (67.5)
During first trimester	4,122 (39.7)	2,745 (36.3)	3,424 (36.3)	2,196 (32.5)
Pregnancy outcome				
Delivered	9,710 (93.6)	7,071 (93.5)	N/A	N/A
Loss	666 (6.4)	489 (6.5)	N/A	N/A
Neonatal sex				
Female	N/A	N/A	4,593 (48.7)	3,260 (48.2)
Male	N/A	N/A	4,842 (51.3)	3,499 (51.8)
Birth plurality				
Singleton	N/A	N/A	9,159 (97.1)	6,574 (97.3)
Multiple	N/A	N/A	276 (2.9)	185 (2.7)
Maternal age at estimated due date (y)				
Younger than 35*	9,600 (92.5)	7,010 (92.7)	N/A	N/A
35 or older*	776 (7.5)	550 (7.3)	N/A	N/A
20–40†	10,017 (96.5)	7,229 (95.6)	N/A	N/A
Younger than 20†	303 (2.9)	266 (3.5)	N/A	N/A
Older than 40†	56 (0.5)	65 (0.9)	N/A	N/A
Maternal age at newborn's birth (y)				
Younger than 35	N/A	N/A	8,728 (92.5)	6,273 (92.8)
35 or older	N/A	N/A	707 (7.5)	486 (7.2)
Maternal race or ethnicity				
White non-Hispanic	5,161 (49.7)	3,769 (49.9)	4,649 (49.3)	3,347 (49.5)
Black non-Hispanic	2,520 (24.3)	1,913 (25.3)	2,318 (24.6)	1,715 (25.4)
Hispanic	1,462 (14.1)	1,037 (13.7)	1,339 (14.2)	935 (13.8)
Other or unknown	1,233 (11.9)	841 (11.1)	1,129 (12.0)	762 (11.3)
Maternal service branch				
Army	3,674 (35.4)	2,704 (35.8)	3,352 (35.5)	2,398 (35.5)
Air Force	3,143 (30.3)	2,507 (33.2)	2,810 (29.8)	2,240 (33.1)
Navy or Coast Guard	2,756 (26.6)	1,745 (23.1)	2,559 (27.1)	1,574 (23.3)
Marine Corps	803 (7.7)	604 (8.0)	714 (7.6)	547 (8.1)
Maternal marital status				
Married	7,465 (71.9)	5,451 (72.1)	6,838 (72.5)	4,891 (72.4)
Unmarried	2,911 (28.1)	2,109 (27.9)	2,597 (27.5)	1,868 (27.6)
Maternal military rank				
Enlisted	8,946 (86.2)	6,569 (86.9)	8,096 (85.8)	5,866 (86.8)
Officer	1,430 (13.8)	991 (13.1)	1,339 (14.2)	893 (13.2)
Maternal military occupation				
Other or unknown	7,788 (75.1)	5,550 (73.4)	7,045 (74.7)	4,969 (73.5)
Health care	2,099 (20.2)	1,556 (20.6)	1,941 (20.6)	1,401 (20.7)
Combat	489 (4.7)	454 (6.0)	449 (4.8)	389 (5.8)

N/A, not applicable.
* Younger than 35 and 35 or older categories are for the pregnancy loss and preterm labor models.
† 20–40, younger than 20, and older than 40 categories are for the preeclampsia or eclampsia model.

influenza vaccine-exposed pregnancies (adjusted hazard ratio [HR] 0.97, 95% confidence interval [CI] 0.86–1.09) when adjusted for maternal age, race and ethnicity, service branch, marital status, and military rank and occupation. Pregnancies among women aged 35 years or older and unmarried women had an increased risk of pregnancy loss, whereas women serving in the Navy or Coast Guard had a decreased risk of pregnancy loss. In the preeclampsia or eclampsia model (n=16,886), there were no significant

differences in preeclampsia or eclampsia rates between the vaccine groups (rate among pandemic H1N1 vaccine-exposed group=5.8%; rate among 2008–2009 seasonal influenza vaccine-exposed group=5.2%; adjusted HR 1.10, 95% CI 0.97–1.26) when adjusted for maternal age, race and ethnicity, service branch, marital status, military rank and occupation, and birth plurality. Pregnancies with a multiple gestation and those among black non-Hispanic women and women serving in the Navy or Coast Guard had a significantly increased risk of diagnosis. Pregnancies among Hispanic women and those with an officer rank had a significantly decreased risk of preeclampsia or eclampsia. Finally, in the preterm labor model (n=15,535), there was no significant difference in preterm labor rates between the exposure groups (rate among pandemic H1N1 vaccine-exposed group=6.5%; rate among 2008–2009 seasonal influenza vaccine-exposed group=6.2%; adjusted HR 1.04, 95% CI 0.91–1.18) when adjusted for maternal age, race and ethnicity, service branch, marital status, and military rank and occupation. Pregnancies among unmarried women (and black non-Hispanic women) had an increased risk of preterm labor.

As a result of the pandemic H1N1 vaccine-exposed pregnancies, 9,435 liveborn neonates with adequate identifying information were included in the birth defect, fetal growth problem, and male-to-female sex ratio analyses and, after excluding multiples, 8,598 in the preterm birth analysis. Among these newborns, 533 (6.2%) were born preterm, 201 (2.1%) had a major birth defect identified at birth, 241 (2.6%) were diagnosed with fetal growth problems, and the male-to-female sex ratio was 1.05. For comparison, 6,759 newborns born as a result of seasonal influenza vaccine-exposed pregnancies were identified for the birth defect, fetal growth problem, and male-to-female sex ratio models and, after excluding multiples, 6,118 for the preterm birth model; 388 (6.3%) were preterm, 132 (2.0%) had a major birth defect identified at birth, 160 (2.4%) had fetal growth problems, and the male-to-female sex ratio was 1.07. Characteristics of the newborns and other pregnancy information are shown in Table 1.

There was no significant difference in preterm birth among newborns born to women who received the pandemic H1N1 vaccine during pregnancy compared with newborns born to women who received seasonal influenza vaccine (adjusted HR 0.98, 95% CI 0.85–1.11) when adjusted for newborn sex, maternal age, race and ethnicity, service branch, marital status, and military rank and occupation. Male newborns and newborns born to black non-Hispanic mothers had a significantly increased risk of being born preterm.

Additionally, the prevalence of birth defects identified among newborns exposed to pandemic H1N1 vaccine prenatally was not significantly different from newborns exposed to seasonal influenza vaccine prenatally (adjusted odds ratio [OR] 1.08, 95% CI 0.87–1.35) when adjusted for vaccination timing, newborn sex, birth plurality, maternal age, race and ethnicity, service branch, marital status, and military rank and occupation. Male newborns and those born to mothers in the Navy or Coast Guard had a significantly increased odds of being diagnosed with a birth defect. Likewise, newborns exposed to pandemic H1N1 vaccine prenatally were not at increased odds of fetal growth problems compared with newborns exposed to seasonal influenza vaccine prenatally (adjusted OR 1.05, 95% CI 0.86–1.29) when adjusted for vaccination timing, newborn sex, birth plurality, maternal age, race and ethnicity, service branch, marital status, and military rank and occupation. Newborns born as part of a multiple gestation and those born to black non-Hispanic mothers, Hispanic mothers, and Navy or Coast Guard mothers were at increased odds of having fetal growth problems. Male newborns were at decreased odds of having fetal growth problems. The male-to-female sex ratio was not significantly different between newborns exposed to the pandemic H1N1 vaccine during gestation and newborns exposed to seasonal influenza vaccine during gestation (adjusted OR 0.98, 95% CI 0.92–1.05) when adjusted for vaccination timing, birth plurality, maternal age, race and ethnicity, service branch, marital status, and military rank and occupation.

DISCUSSION

This study of 10,376 pregnancies among active-duty U.S. military women who received the pandemic H1N1 vaccination during pregnancy and the 9,435 identified newborns born as a result of these pregnancies revealed no evidence for either adverse maternal or newborn outcomes when compared with those exposed to seasonal influenza vaccine during the prior season. These findings provide timely reassurance of the safety of the 2009–2010 pandemic H1N1 vaccine when administered during pregnancy and should be used to enhance the use of influenza vaccines among this highly vulnerable population.

Since 2004, both the Advisory Committee on Immunization Practices and the American College of Obstetricians and Gynecologists have recommended inactivated injectable influenza vaccine for all pregnant women (regardless of trimester).[27] The basis for this recommendation is that pregnancy places women and

their fetuses at increased risk for morbidity and mortality from influenza infection, especially during pandemics,[2,28] and vaccination provides the best protection against infection.[29] Furthermore, transplacental transfer of antibodies may protect the neonate during the newborn period, a time of increased vulnerability to infection.[29] Despite these scientific data, influenza vaccine uptake among pregnant women remains low,[30] perhaps in part as a result of concerns regarding safety.[31]

Data regarding the safety of seasonal influenza vaccination have revealed no significant adverse maternal or fetal outcomes to date.[32] However, the pandemic H1N1 vaccine provoked concerns regarding adverse events given the prior safety issues associated with the 1976 swine influenza vaccine.[6] Our results provide critical data on the safety of pandemic H1N1 vaccines by studying a large cohort of pregnant women and by using a comparison group of pregnant women exposed to 2008–2009 seasonal influenza vaccination. These data support the use of pandemic H1N1 influenza vaccines among pregnant women.

The high vaccination coverage rate among the women in this cohort (greater than 75–80%) is notable and much higher than the rates generally seen in civilian populations.[30] The compulsory nature of vaccination in the military is undoubtedly largely responsible, but there could also be an element of greater compliance and an overall healthier lifestyle among these military women. In fact, choosing women exposed to seasonal influenza vaccine the year prior as the comparison group, rather than unvaccinated women from the same year, was done to limit inherent health differences between the two groups such as overall health or health attitudes.

There are some strengths and limitations of this study that should be considered. Studies of vaccine safety during pregnancy are often limited by small sample size, but this study included over 10,000 pandemic H1N1 vaccine-exposed pregnancies and over 7,000 seasonal influenza vaccine-exposed pregnancies as well as over 9,000 and nearly 7,000 newborns, respectively, resulting from these pregnancies. Although pregnant women were not "enrolled" in the study and it instead relied on electronic medical record data, any misclassification bias in such data is likely to be nondifferential. Additionally, electronic data were available in a reasonable amount of time, allowing for interim analyses of the data and dissemination of the reassuring results to Department of Defense leadership and national vaccine agencies while the vaccination campaign was continuing. Potential limitations included that classification of the exposure status relied on estimations of pregnancy onset and estimated gestational age, and outcomes were classified using complex algorithms and combinations of ICD-9-CM codes, but medical record chart reviews conferred a high level of confidence in the findings. The comparison group of women vaccinated with seasonal influenza during the 2008–2009 influenza season was carefully chosen, but it is possible that these women had an increased rate of adverse outcomes, making a difference more difficult to detect. The relatively low rates of each outcome overall, however, make this possibility unlikely. We did not independently assess pandemic H1N1 vaccinated women by their 2009–2010 seasonal influenza vaccine status. As anticipated, there were a small number of pregnancies with unknown outcomes, probably as a result of women not seeking medical care or using non-Department of Defense–sponsored health care. These relatively low numbers, however, would be unlikely to significantly affect the results.

The results of this study add to the growing body of literature demonstrating the safety of the pandemic H1N1 vaccine when administered during pregnancy and should be used to encourage increased use of influenza vaccines among the highly vulnerable pregnant population.

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REPORT DOCUMENTATION PAGE

1. REPORT DATE (DD MM YY)
03 05 12

2. REPORT TYPE
Journal Submission

3. DATES COVERED (from – to)
2008–2010

4. TITLE
Safety of the Pandemic H1N1 Influenza Vaccine among Pregnant U.S. Military Women and Their Newborns

5a. Contract Number:
5b. Grant Number:
5c. Program Element Number:
5d. Project Number:
5e. Task Number:
5f. Work Unit Number:

6. AUTHORS
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8. PERFORMING ORGANIZATION REPORT NUMBER
Report No. 12-34

8. SPONSORING/MONITORING AGENCY NAMES(S) AND ADDRESS(ES)
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10. SPONSOR/MONITOR'S ACRONYM(S)
NMRC/BUMED

11. SPONSOR/MONITOR'S REPORT NUMBER(s)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution is unlimited.

13. SUPPLEMENTARY NOTES
Obstetrics and Gynecology, 2013, 12(3), 511-18

14. ABSTRACT

A pandemic influenza A virus (pH1N1) emerged in April 2009, preferentially affecting pregnant women and their fetuses. Data regarding the safety of pH1N1 vaccination on both maternal and fetal outcomes are important. Pregnancies and pH1N1 vaccination status were identified among active-duty US military women (October 2009–June 2010). Maternal and infant outcomes were assessed and compared with pregnant women vaccinated with seasonal influenza vaccine (October 2008–June 2009). There were 10 896 pregnancies exposed to pH1N1 vaccine. Rates of pregnancy loss, preeclampsia/eclampsia, and preterm labor were similar to rates seen among seasonal influenza vaccine-exposed pregnancies from the previous year. Analyses of the 9435 infants born as a result of these pregnancies revealed no differences in the rates of preterm birth, birth defects, fetal growth problems, or the male:female sex ratio compared with infants exposed to seasonal influenza vaccine during gestation. Rates of all outcomes were lower or similar to overall rates within the general population. There were no identified adverse pregnancy or infant health outcomes associated with pH1N1 vaccination during pregnancy noted among our cohort. These findings are important for determining the safety of pH1N1 vaccination and should be used to encourage increased vaccine coverage among pregnant women.

15. SUBJECT TERMS
H1N1, influenza, vaccination, pregnancy, military, adverse events, maternal outcomes, infant outcomes

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	18a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			Commanding Officer
UNCL	UNCL	UNCL	UNCL	8	18b. TELEPHONE NUMBER (INCLUDING AREA CODE) COMM/DSN: (619) 553-8429